

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Commissioner
 US Department of Commerce
 United States Patent and Trademark
 Office, PCT
 2011 South Clark Place Room
 CP2/5C24
 Arlington, VA 22202
 ETATS-UNIS D'AMERIQUE
 in its capacity as elected Office

Date of mailing (day/month/year) 18 June 2001 (18.06.01)	
International application No. PCT/US00/26634	Applicant's or agent's file reference 00786/376WO1
International filing date (day/month/year) 28 September 2000 (28.09.00)	Priority date (day/month/year) 30 September 1999 (30.09.99)
Applicant ROSENBAUM, Jerrold	

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:

30 March 2001 (30.03.01)

☐ in a notice effecting later election filed with the International Bureau on:2. The election ☒ was☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO
 34, chemin des Colombettes
 1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

Olivia TEFY

Telephone No.: (41-22) 338.83.38

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/26634**A. CLASSIFICATION OF SUBJECT MATTER**

IPC(7) : A01N 43/78

US CL : 514/367

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/367

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Please See Extra Sheet.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Database Medline on STN, Department of Neuropharmacology, Scripps Research Institute, (La Jolla, CA), No. 97387623, CAINE, S. B., "D3 Receptor Test in vivo Predicts Decreased Cocaine Self-Administration in Rats", abstract, Neuroreport, 8(9-10), pp. 2373-2377, 07 July 1997.	1-4



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
A document defining the general state of the art which is not considered to be of particular relevance	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
E earlier document published on or after the international filing date	*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*G* document member of the same patent family
O document referring to an oral disclosure, use, exhibition or other means	
P document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

27 NOVEMBER 2000

Date of mailing of the international search report

04 JAN 2001

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

Facsimile No. (703) 305-3230

Authorized officer
Dwight C. Jones
DWAYNE C. JONES

Telephone No. (703) 308-1235

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/26634

B. FIELDS SEARCHED

Electronic data bases consulted (Name of data base and where practicable terms used):

REGISTRY, MEDLINE, EMBASE, WPIDS, DRUGU, BIOSIS, CAPLUS structure search with the following terms
pramipexole?, drugs of abuse, drug dependence, mirapex, snd919 or snd 919, stimulant/(3a)(depend? or addict?),
lamotrigine.

RECEIVED
PATENT COOPERATION TREATY

OCT 03 2002

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

REC'D 11 APR 2002

WIPO

PCT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 00786/376/WO1	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/US00/26634	International filing date (day/month/year) 28 SEPTEMBER 2000	Priority date (day/month/year) 30 SEPTEMBER 1999
International Patent Classification (IPC) or national classification and IPC IPC(7): A01N 43/78 and US Cl.: 514/367		
Applicant THE GENERAL HOSPITAL CORPORATION		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 3 sheets.

☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority. (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 0 sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of report with regard to novelty, inventive step or industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability, citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand 30 MARCH 2001	Date of completion of this report 27 FEBRUARY 2002
Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks	Authorized officer Dorothy Lawrence To

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US00/26634

I. Basis of the report

1. With regard to the **elements** of the international application:*☒ the international application as originally filed☒ the description:

pages 1-10 , as originally filed
pages NONE , filed with the demand
pages NONE ; filed with the letter of _____

☒ the claims:

pages 11 , as originally filed
pages NONE , as amended (together with any statement) under Article 19
pages NONE , filed with the demand
pages NONE , filed with the letter of _____

☒ the drawings:

pages 1 , as originally filed
pages NONE , filed with the demand
pages NONE , filed with the letter of _____

☒ the sequence listing part of the description:

pages NONE , as originally filed
pages NONE , filed with the demand
pages NONE , filed with the letter of _____

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language _____ which is:

- ☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).
☐ the language of publication of the international application (under Rule 48.3(b)).
☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in printed form.
☐ filed together with the international application in computer readable form.
☐ furnished subsequently to this Authority in written form.
☐ furnished subsequently to this Authority in computer readable form.
☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☒ The amendments have resulted in the cancellation of:

- ☒ the description, pages NONE
☒ the claims, Nos. NONE
☒ the drawings, sheets/fig NONE

5. ☐ This report has been drawn as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

* Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).

**Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US00/26634

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. statement

Novelty (N)

Claims NONE

YES

Claims 1-4

NO

Inventive Step (IS)

Claims NONE

YES

Claims 1-4

NO

Industrial Applicability (IA)

Claims 1-4

YES

Claims NONE

NO

2. citations and explanations (Rule 70.7)

Claims 1-4 lack novelty under PCT Article 33(2) as being anticipated by CAIN et al. of Database Medline on STN No. 97387623. CAIN et al. teach of pramipexole as a pharmacotherapy for cocaine abuse and dependence.

----- NEW CITATIONS -----

NONE

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
5 April 2001 (05.04.2001)

PCT

(10) International Publication Number
WO 01/22820 A1

- (51) International Patent Classification⁷: **A01N 43/78**
- (21) International Application Number: **PCT/US00/26634**
- (22) International Filing Date:
28 September 2000 (28.09.2000)
- (25) Filing Language: **English**
- (26) Publication Language: **English**
- (30) Priority Data:
60/156,860 30 September 1999 (30.09.1999) **US**
- (71) Applicant (for all designated States except US): **THE GENERAL HOSPITAL CORPORATION [US/US]; 55 Fruit Street, Boston, MA 02114 (US).**
- (72) Inventor; and
- (75) Inventor/Applicant (for US only): **ROSENBAUM, Jerrold [US/US]; 587 Walnut Street, Newton, MA 02460 (US).**
- (74) Agent: **ELBING, Karen, L.; Clark & Elbing LLP, 176 Federal Street, Boston, MA 02110-2214 (US).**
- (81) Designated States (*national*): **AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.**
- (84) Designated States (*regional*): **ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).**
- Published:**
— *With international search report.*
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

(54) Title: **USE OF PRAMIPEXOLE AS A TREATMENT FOR COCAINE CRAVING**

(57) Abstract: Disclosed herein are methods for reducing stimulant dependency or craving, involving administration of a therapeutic agent.

WO 01/22820 A1

USE OF PRAMIPEXOLE AS A TREATMENT FOR COCAINE CRAVING

5

Background of the Invention

This invention relates to methods for the treatment of cocaine craving.

Cocaine is a highly addictive psychostimulant that causes sensations of euphoria and craving, resulting in physiological as well as psychological damage. Although cocaine use leads to a multitude of physiological complications, its primary target of action is the central nervous system. Cocaine withdrawal following abstinence causes, among other symptoms, an intense craving for the abused drug, which in turn frequently results in the relapse into renewed drug use. Epidemiological studies point to a high incidence of multiple substance abuse among cocaine users, a finding that has significant societal and medical repercussions.

10

15

To date, approved pharmacotherapies for cocaine abuse and dependence have proven scarce despite the acute need for such therapies.

20

Summary of the Invention

In general, the invention features methods for treating stimulant dependencies, such as cocaine craving, by administering a therapeutically-effective amount of a dopamine agonist, for example, pramipexole.

In one aspect, the invention provides a method of treating a patient

therapeutically-effective amount of pramipexole to the patient. In preferred embodiments of this aspect, the stimulant dependency is a stimulant craving and the stimulant is cocaine.

In a related aspect, the invention provides a method of treating a
5 human diagnosed with cocaine craving by administering a therapeutically-effective amount of pramipexole to the human.

In preferred embodiments of both of the above aspects of the invention, the method further includes administering a therapeutically-effective amount of an antidepressant or an anticonvulsant, for example,
10 lamotrigine.

By "treating" is meant the medical management of a patient with the intent that a cure, amelioration, or prevention of a dependency or a relapse or associated disease, pathological condition, or disorder will result. This term includes active treatment, that is, treatment directed specifically
15 toward improvement of the dependency or associated cure of a disease, pathological condition, or disorder, and also includes causal treatment, that is, treatment directed toward removal of the cause of the dependency or associated disease, pathological condition, or disorder. In addition, this term includes palliative treatment, that is, treatment designed for the relief
20 of symptoms rather than the curing of the dependency, disease, pathological condition, or disorder; preventive treatment, that is, treatment directed to prevention of the dependency or associated disease, pathological condition, or disorder; and supportive treatment, that is, treatment employed to supplement another specific therapy directed toward the improvement of the
25 dependency or associated disease, pathological condition, or disorder. The

term "treating" also includes symptomatic treatment, that is, treatment

By "stimulant" is meant any substance that temporarily increases functional activity, and preferably cardiac, respiratory, cerebral, nervous, vascular, motor, or vasomotor functional activity. Preferred stimulants include, without limitation, cocaine, amphetamines, methamphetamine, and
5 methylphenidate.

By "therapeutically-effective amount" is meant an amount of a pramipexole compound sufficient to produce a healing, curative, or ameliorative effect either in the treatment of a stimulant dependency or in the symptoms of a stimulant dependency, for example, cocaine craving.

10 By "dependency" is meant any form of behavior that indicates an altered or reduced ability to make decisions resulting, at least in part, from the use of stimulants. Representative forms of dependency behavior may take the form of antisocial, inappropriate, or illegal behavior and include those behaviors directed at the desire, planning, acquiring, and use of
15 stimulants. This term also includes the psychic craving for a drug that may or may not be accompanied by a physiological dependency, as well as a state in which there is a compulsion to take a drug, either continuously or periodically, in order to experience its psychic effects or to avoid the discomfort of its absence. Forms of "dependency" include habituation, that
20 is, an emotional or psychological dependence on a compound to obtain relief from tension and emotional discomfort, as well as physical or physiological dependence, that is, use of a compound to prevent withdrawal symptoms.

By "craving" is meant a behavior that reflects a consuming desire,
25 longing, or yearning for a stimulant. This term may refer to aspects of behaviors that are components of a dependency.

The present invention provides a number of advantages.

Importantly, it provides one of the first therapeutics for the treatment of

stimulant cravings (such as cocaine craving). In addition, the pramipexole utilized herein is non-toxic, is pharmacokinetically understood, and is known to be well tolerated by humans, as is evidenced by its approval for the treatment of Parkinson's Disease.

5 Brief Description of the Drawings

Figure 1 is a schematic illustration of the molecular structure of pramipexole, marketed as Mirapex in the United States.

Detailed Description of the Invention

10 The invention described herein features methods involving the administration of pramipexole (or other dopamine-D3/D2 agonists) for the treatment of stimulant dependency, and preferably for the treatment of cocaine craving and its symptoms, as well as cocaine dependency and associated self-destructive behaviors.

15 Described below is an example of the successful use of pramipexole for the treatment of cocaine craving and related symptoms. This example is provided for the purpose of illustrating the invention, and should not be construed as limiting.

Treatment of Cocaine Craving Using Pramipexole

20 Mr. A, a 34 year-old single, successful business man, was referred for evaluation of possible bipolar disorder. Currently depressed, he had in the previous year brought financial ruin on himself by a pattern of cocaine freebasing and sexual and other extravagance that absorbed nearly one million dollars.

25 Along with current major depression, persisting cocaine craving but rare use and a question of past primary or secondary (to substance abuse)

mania, he manifested an extraordinary movement disorder with constant restlessness and thrashing of his legs, leaving the inner aspects of his knees and thighs bruised and discolored with hematomas in various stages of evolution and resolution.

5 For the restless legs, he had consulted a neurologist who diagnosed "pre-parkinsonism" presumed secondary to neurological damage from cocaine. The disfiguring movements limited his ability to return to and conduct business.

Previously, he had failed to respond to or tolerate most of the new
10 generation of antidepressants. Treatment was begun with lamotrigine up to 200 mg with modest improvement in mood. Given his severe restless legs syndrome and persisting depression, pramipexole was added, titrated to 1.5 mg a day in divided doses.

In response to this treatment, his leg movements quieted
15 substantially, his mood brightened, and he reported that these were the first days in a year that he awoke without craving cocaine, a benefit sustained for one year on this drug, combined with 75 mg of lamotrigine. During the subsequent year, Mr. A. reported one day of non-compliance when he was out of town without his medication. That night, for the first time, he dreamt
20 about cocaine and the next day experienced a renewed craving on awakening which resolved when treatment was restored.

Although he faces an array of financial and business challenges, his mood following treatment is nearly euthymic, his leg movements at worst resemble mild restlessness, and his cocaine craving remains abolished.

25 These dramatic results demonstrate that dopamine agonists, like pramipexole, represent treatments for cocaine craving, and may be particularly useful for patients with comorbid refractory depression

Pramipexole and Other Dopamine Agonists

The synthesis of pramipexole is described in U.S. Patent No. 4,886,812 and European Patent 186 087. Pramipexole is a non-ergot derivative which may be used at a range of between about 1.5 mg to 6.0 mg per day, and is preferably administered between about 1.5 mg and 4.5 mg per day. Higher dosages may be used with the concomitant risk of potential side effects.

Other formulations for treatment or prevention of stimulant dependency or craving, such as cocaine craving, as described herein, may take the form of a dopamine agonist compound that may be combined with a pharmaceutically-acceptable diluent, carrier, stabilizer, or excipient. Conventional pharmaceutical practice is employed to provide suitable formulations or compositions to administer such compositions to patients. Oral administration is preferred, but any other appropriate route of administration may be employed, for example, parenteral, intravenous, subcutaneous, intramuscular, intracranial, intraorbital, ophthalmic, intraventricular, intracapsular, intraspinal, intracisternal, intraperitoneal, intranasal, or aerosol administration. Therapeutic formulations may be in the form of liquid solutions or suspensions (as, for example, for intravenous administration); for oral administration, formulations may be in the form of liquids, tablets or capsules; and for intranasal formulations, in the form of powders, nasal drops, or aerosols.

Methods well known in the art for making formulations are described, for example, in "Remington: The Science and Practice of Pharmacy" (19th ed.) ed. A.R. Gennaro AR., 1995, Mack Publishing Company, Easton, PA. Formulations for parenteral administration may, for

example, contain excipients, sterile water, saline, polyalkylene glycols such as polyethylene glycol, oils of vegetable origin, or hydrogenated naphthalenes.

If desired, slow release or extended release delivery systems may be utilized. Biocompatible, biodegradable lactide polymer, lactide/glycolide copolymer, or polyoxyethylene-polyoxypropylene copolymers may be used to control the release of the compounds. Other potentially useful parenteral delivery systems include ethylene-vinyl acetate copolymer particles, osmotic pumps, implantable infusion systems, and liposomes. Formulations for inhalation may contain excipients, for example, lactose, or may be aqueous solutions containing, for example, polyoxyethylene-9-lauryl ether, glycocholate and deoxycholate, or may be oily solutions for administration in the form of nasal drops, or as a gel.

In general, a dopamine agonist for use in the methods of the invention is administered at a dosage appropriate to the effect to be achieved and is typically administered in unit dosage form. As noted above, the preferred route of administration for most indications is oral.

An effective quantity of a dopamine agonist-containing compound of the invention is employed to treat the stimulant dependency or craving, for example, cocaine craving as described herein. The exact dosage of the compound may be dependent, for example, upon the age and weight of the recipient, the route of administration, and the severity and nature of the symptoms to be treated. In general, the dosage selected should be sufficient to prevent, ameliorate, or treat the condition, or one or more symptoms thereof without producing significant toxic or undesirable side effects

Combination with Other Therapeutics

One particular source of pramipexole is Pharmacia & Upjohn, Inc. which markets Mirapex (Pramipexole Dihydrochloride) tablets which have the molecular structure shown in Figure 1. Examples of other dopamine agonists include, but are not limited to, amantadine, bromocriptine, cabergoline, lisuride, pergolide, ropinirole, quinpirole, or quinelorane. Pramipexole, or any other dopamine agonist, may be administered as a monotherapy, or in combination with other compounds, for the treatment of multiple substance abuse or other physiological or psychological conditions.

10 In one particular example, the dopamine agonist (e.g. pramipexole) may be administered in combination with an antidepressant, anticonvulsant, antianxiety, antimanic, antipsychotic, antiobsessional, sedative-hypnotic, or stimulant medication. Examples of these medications include, but are not limited to, the antianxiety medications alprazolam, buspirone hydrochloride, 15 chlordiazepoxide, chlordiazepoxide hydrochloride, clorazepate dipotassium, desipramine hydrochloride, diazepam, halazepam, hydroxyzine hydrochloride, hydroxyzine pamoate, lorazepam, meprobamate, oxazepam, prazepam, prochlorperazine maleate, prochlorperazine, prochlorperazine edisylate, and trimipramine maleate; the anticonvulsants amobarbital, 20 amobarbital sodium, carbamazepine, chlordiazepoxide, chlordiazepoxide hydrochloride, clorazepate dipotassium, diazepam, divalproex sodium, ethosuximide, ethotoin, gabapentin, lamotrigine, magnesium sulfate, mephenytoin, mephobarbital, methsuximide, paramethadione, pentobarbital sodium, phenacemide, phenobarbital, phenobarbital sodium, phensuximide, 25 phenytoin, phenytoin sodium, primidone, secobarbital sodium, trimethadione, valproic acid, and clonazepam; the antidepressants amitriptyline hydrochloride, amoxapine, bupropion hydrochloride, clomipramine hydrochloride, desipramine hydrochloride, doxepin

hydrochloride, fluoxetine, fluvoxamine, imipramine hydrochloride,
imipramine pamoate, isocarboxazid, lamotrigine, maprotiline
hydrochloride, nortriptyline hydrochloride, paroxetine hydrochloride,
phenelzine sulfate, protriptyline hydrochloride, sertraline hydrochloride,
5 tranylcypromine sulfate, trazodone hydrochloride, trimipramine maleate,
and venlafaxine hydrochloride; the antimanic medications lithium carbonate
and lithium citrate; the antiobsessional medications fluvoxamine, and
clomipramine hydrochloride; the antipsychotic medications acetophenazine
maleate, chlorpromazine hydrochloride, chlorprothixene, chlorprothixene
10 hydrochloride, clozapine, fluphenazine decanoate, fluphenazine enathrate,
fluphenazine hydrochloride, haloperidol decanoate, haloperidol, haloperidol
lactate, lithium carbonate, lithium citrate, loxapine hydrochloride, loxapine
succinate, mesoridazine besylate, molindone hydrochloride, perphenazine,
pimozide, prochlorperazine maleate, prochlorperazine, prochlorperazine
15 edisylate, promazine hydrochloride, risperidone, thioridazine, thioridazine
hydrochloride, thiothixene, thiothixene hydrochloride, and trifluoperazine
hydrochloride; the sedative-hypnotic medications amobarbital, amobarbital
sodium, aprobarbital, butabarbital, chloral hydrate, chlordiazepoxide,
chlordiazepoxide hydrochloride, clorazepate dipotassium, diazepam,
20 diphenhydramine, estazolam, ethchlorvynol, flurazepam hydrochloride,
glutethimide, hydroxyzine hydrochloride, hydroxyzine pamoate, lorazepam,
methotrimeprazine hydrochloride, midazolam hydrochloride, non
prescription, oxazepam, pentobarbital sodium, phenobarbital, phenobarbital
sodium, quazepam, secobarbital sodium, temazepam, triazolam, and
25 zolpidem tartrate; and the stimulants dextroamphetamine sulfate,
methamphetamine hydrochloride, methylphenidate hydrochloride and

Other Embodiments

All publications and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each independent publication or patent application was specifically and
5 individually indicated to be incorporated by reference.

While the invention has been described in connection with specific embodiments thereof, it will be understood that it is capable of further modifications and this application is intended to cover any variations, uses, or adaptations of the invention following, in general, the principles of the
10 invention and including such departures from the present disclosure that come within known or customary practice within the art to which the invention pertains and may be applied to the essential features hereinbefore set forth, and follows in the scope of the appended claims.

Other embodiments are within the claims.

Claims

1. A method of treating a human with a stimulant dependency, said method comprising administering to said human a therapeutically-effective amount of pramipexole.
- 5 2. The method of claim 1, wherein said stimulant dependency involves a stimulant craving.
3. The method of claim 1, wherein said stimulant is cocaine.
4. A method of treating a cocaine craving in a human, said method comprising administering to said human a therapeutically-effective amount
10 of pramipexole.
5. The method of claim 1 or 4, wherein said method further comprises administering to said human a therapeutically-effective amount of an antidepressant.
6. The method of claim 1 or 4, wherein said method further
15 comprises administering to said human a therapeutically-effective amount of an anticonvulsant.
7. The method of claim 6, wherein the anticonvulsant is lamotrigine.

1/1

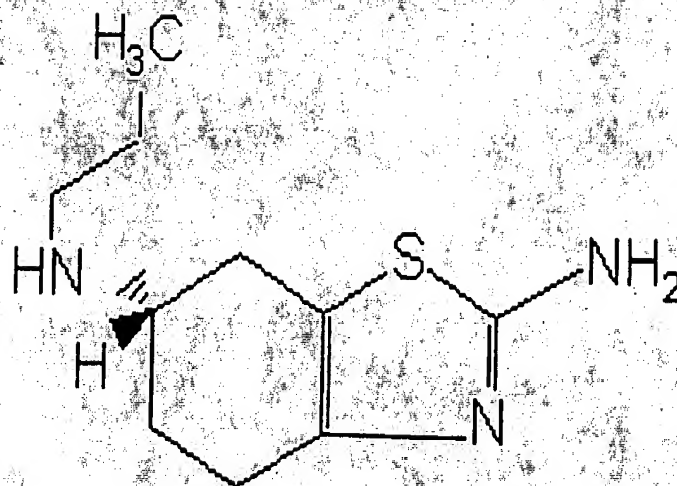


FIGURE 1

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US00/26634

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A01N 43/78

US CL : 514/367

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/367

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
NONEElectronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Please See Extra Sheet.**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Database Medline on STN, Department of Neuropharmacology, Scripps Research Institute, (La Jolla, CA), No. 97387623, CAINE, S. B., "D3 Receptor Test in vivo Predicts Decreased Cocaine Self-Administration in Rats", abstract, Neuroreport, 8(9-10), pp. 2373-2377, 07 July 1997.	1-4

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
A document defining the general state of the art which is not considered to be of particular relevance	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
E earlier document published on or after the international filing date	*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*G* document member of the same patent family
O document referring to an oral disclosure, use, exhibition or other means	
P document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

27 NOVEMBER 2000

Date of mailing of the international search report

04 JAN 2001

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US00/26634

B. FIELDS SEARCHED

Electronic data bases consulted (Name of data base and where practicable terms used):

REGISTRY, MEDLINE, EMBASE, WPIDS, DRUGU, BIOSIS, CAPLUS structure search with the following terms
pramipexole?, drugs of abuse, drug dependence, mirapex, snd919 or snd 919, stimulant#(3a)(depend? or addict?),
lamotrigine.

THE MERCK INDEX

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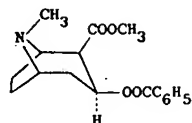
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(1979). Biosynthesis: E. Leete, *Chem. Commun.* 1980, 1170.



Monoclinic tablets from alcohol, mp 98°. Volatile, esp above 90°, but the sublimate is not crystalline. bp_{0.1} 187-188°. [α]_D²⁰ -35° (50% alcohol); [α]_D²⁰ -16° (c = 4 in chloroform). Aq solns are alkaline to litmus. pK at 15° = 5.59. Absorption spectrum: Dobbie, Fox, *J. Chem. Soc.* 103, 1194 (1913); Fischer, *Arch. Exp. Pathol. Pharmacol.* 170, 610 (1933). One gram dissolves in 600 ml water, 270 ml water at 80°, 6.5 ml alcohol, 0.7 ml chloroform, 3.5 ml ether, 12 ml oil turpentine, 12 ml olive oil, 30-50 ml liquid petrolatum; also sol in acetone, ethyl acetate, carbon disulfide. LD₅₀ i.v. in rats: 17.5 mg/kg, C. L. Rose *et al.*, *J. Lab. Clin. Med.* 15, 731 (1930).

Caution: Abuse leads to habituation or addiction.

USE: The free base is used for ointments and oily solns because of its sol in fats; otherwise the hydrochloride or the sulfate is preferred.

THERAP CAT: Topical anesthetic (narcotic).

THERAP CAT (VET): See Cocaine Hydrochloride.

2412. Cocaine Hydrochloride. Cocaine muriate. C₁₇H₂₁ClNO₄; mol wt 339.81. C 60.08%, H 6.53%, Cl 10.43%, N 4.12%, O 18.83%.

Crystals, granules, or powder; saline, slightly bitter taste; numbs tongue and lips. mp about 195°. [α]_D²⁰ -72° (c = 2 in aq soln pH 4.5). One gram dissolves in 0.4 ml water; 3.2 ml cold, 2 ml hot alcohol; 12.5 ml chloroform. Also sol in glycerol, acetone. Insol in ether or oils. Avoid heat in preparing soln as it decomposes. Preserve in well-closed, light-resistant containers.

Incompat. Calomel, mercuric oxide, silver nitrate, precipitants of alkaloids in general.

Caution: Abuse leads to habituation or addiction.

THERAP CAT: Topical anesthetic.

THERAP CAT (VET): Local anesthetic and CNS stimulant; now used almost exclusively for local anesthesia of the eye.

2413. Cocaine Nitrate. C₁₇H₂₁N₂O₇; mol wt 366.38. C 55.73%, H 6.05%, N 7.65%, O 30.57%. C₁₇H₂₁NO₄·HNO₃. Dihydrate, crystals, mp 58-63°. Freely sol in water or alc; slightly sol in ether. *Keep in a cool place.*

Caution: Abuse leads to habituation or addiction.

THERAP CAT: Topical anesthetic.

2414. Cocaine Sulfate. C₁₇H₂₁NO₆S₂; mol wt 401.43. C 50.86%, H 5.78%, N 3.49%, O 31.88%, S 7.99%.

White, granular, cryst powder. Sol in water or alcohol.

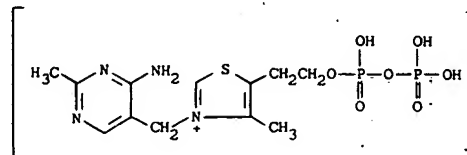
Caution: Abuse leads to habituation or addiction.

THERAP CAT: Topical anesthetic.

THERAP CAT (VET): See Cocaine Hydrochloride.

2415. Cocarboxylase. 3-[(4-Amino-2-methyl-5-pyrimidinyl)methyl]-5-[2-[[hydroxy(phosphonoxy)phosphinyl]oxyethyl]-4-methylthiazolium chloride; thiamine pyrophosphoric acid ester chloride; thiamine pyrophosphate chloride; thiamine diphosphoric acid ester chloride; thiamine diphosphate ester chloride; Bioxilas; Bivitas; Cocalose; Cocarbina; Berolase; Biosyth. C₁₂H₁₉ClN₄O₇P₂S; mol wt 460.76. C 31.28%, H 4.16%, Cl 7.69%, N 12.16%, O 24.31%, P 13.44%, S 6.96%. The coenzyme or prosthetic group of the yeast enzyme carboxylase which is composed of a protein, apocarboxylase, and cocarboxylase. Cocarboxylase is the key substance in biochemical decarboxylation, it catalyzes the decarboxylation of many α-oxo acids. Enzymatic synthesis: Lohmann, Schuster, *Biochem. Z.* 294, 183 (1937); Tauber, *Enzymologia* 2, 171 (1937). Enzymatic synthesis stops when the apoenzyme is satd and is useless for preparative purposes. Chemical synthesis: Weijlard, Tauber, *J. Am. Chem. Soc.* 60, 2263 (1938); Weil-Malherbe, *Biochem. J.* 34, 980 (1940); Weijlard, *J. Am. Chem. Soc.* 63, 1160 (1941); Karrer, Viscontini, *Helv. Chim. Acta* 29, 711 (1946); Galamon, Fili-

powicz, C.A. 69, 19108n (1968). Review of enzyme activity: Ullrich *et al.*, *Vitam. Horm. (New York)* 28, 365 (1970).



Monohydrate, crystals from alc contg some HCl, dec 240-244°. mp 238-240° from abs ethanol. uv max: 242 nm. Soluble in water. pH of 0.3% soln 2.23. The dry substance is very stable. Aq solns are somewhat less stable than solns of thiamine chloride. The free ester forms a stable tetrahydrate, C₁₂H₁₈N₄O₇P₂S·4H₂O, dec 220-225°. Prepn: Wenz, Göttmann, Koop, U.S. pat. 2,991,284 (1961 to E. Merck).

2416. Cocculus. Fish-berry; Indian berry; *Cocculus indicus*; oriental berry. Dried fruit of *Anamirta cocculus* (L.) Wight & Arn., *Menispermaceae*. *Habit.* East Indies, Malay Archipelago. *Constit.* Menispermene, paramenispermene, about 1% picrotoxin, picrotoxic acid, cocculine alkaloid, about 50% fat. *Poisonous!*

THERAP CAT: Central and respiratory stimulant.

2417. Cochineal. The dried female insect, *Coccus cacti* L., enclosing the young larvae. *Habit.* Mexico, Central America; cultivated in West Indies, Canary Islands, Algiers, and Southern Spain. About 70,000 insects to 1 lb. *Constit.* About 10% carminic acid, about 2% coccerin (a wax), about 10% fat. The coloring matter—alkali carminate—is contained only in the fatty parts of the insect and in the yolk of the eggs, to the extent of 10-14%.

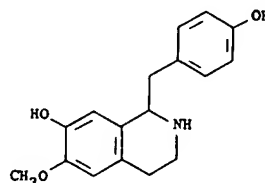
USE: Coloring food products and toilet preparations; the source of carmine and carminic acid for manuf red and pink inks and lakes.

2418. Cocillana. Dried bark of *Guarea rusbyi* (Britt.) Rusby, *Meliaceae*. *Habit.* Bolivia. *Constit.* Rusbyine, about 2.5% resins, about 2.5% fat, tannin.

THERAP CAT: Expectorant.

THERAP CAT (VET): Has been used as an expectorant.

2419. Coclaurine. (S)-1,2,3,4-Tetrahydro-1-[(4-hydroxyphenyl)methyl]-6-methoxy-7-isoquinolinol; 1-(p-hydroxybenzyl)-6-methoxy-7-hydroxy-1,2,3,4-tetrahydroisoquinoline; machiline. C₁₇H₁₉NO₃; mol wt 285.33. C 71.56%, H 6.71%, N 4.91%, O 16.82%. Isolated as the racemate from species of *Machilus* (*Lauraceae*) and *Cocculus* (*Menispermaceae*). First isoln from *C. laurifolius* D.C. believed to be of the d-form: Kondo, Kondo, *J. Pharm. Soc. Japan* no. 524, 876 (1925), C.A. 20, 6047 (1926); see also Johns *et al.*, *Aust. J. Chem.* 20, 1729 (1967). Structure: Kondo, Kondo, *J. Pharm. Soc. Japan* 48, 1156 (1928); Tomita, Kusuda, *ibid.* 72, 280 (1952). Synthesis: Kratzl, Billek, *Monatsh.* 82, 568 (1951); Finkelstein, *J. Am. Chem. Soc.* 73, 550 (1951). Identity with machiline: Tomita *et al.*, *J. Pharm. Soc. Japan* 83, 218 (1963), C.A. 59, 2874a (1963). Crystal structure and absolute configuration: Fridrichsons, Mathieson, *Tetrahedron* 24, 5785 (1968).



Plates, tablets from alc, mp 220-221°. Sol in hot alc, hot acetone; slightly sol in water, alc, chloroform, ether, acetone; practically insol in benzene, petr ether.

Hydrochloride, C₁₇H₁₉NO₃·HCl, crystals, mp 263-264°.

2420. Cocoa. A powder prepd from the roasted and

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cocaine

$C_{17}H_{21}NO_4$; Benzoylmethylecgonine; a crystalline alkaloid obtained from the leaves of Erythroxylon coca (family Erythroxylaceae) and other species of Erythroxylon, or by synthesis from ecgonine or its derivatives; a potent central nervous system stimulant, vasoconstrictor, and topical anesthetic, widely abused as a euphoriant and associated with the risk of severe adverse physical and mental effects. The coca bush is indigenous to Bolivia and Peru, where for centuries natives have chewed its leaves along with limestone pellets or plant ashes in order to withstand hunger, thirst, and fatigue. During the 19th century cocaine was widely used in medicine as a stimulant, antidepressant, and topical anesthetic, but because of its strong potential for inducing dependency it is no longer administered systemically. Its popularity as a recreational drug waned slightly after amphetamines became available in the 1920s but returned in the 1960s. Cocaine is generally sold on the street as the hydrochloride salt, a fine white powder known as "coke," "C," "snow," "flake," or "blow." Street dealers cut or adulterate it with inert substances such as cornstarch, talcum powder, and sugar, or with active drugs such as procaine and benzocaine. In powder form it is usually "snorted" into the nostrils, although it may also be absorbed through the buccal, vaginal, or rectal mucosa or injected. A smokable form of cocaine can be prepared from the hydrochloride by a process called "free-basing." Production of pure free-base cocaine is hazardous because it employs highly flammable solvents. The drug commonly called "crack" is a crude form of free base prepared from cocaine hydrochloride with ammonia or sodium bicarbonate and water. The hardened product of this process is cracked into irregular fragments called "rock," "ready rock," "french fries," or "teeth." Street use of crack exploded upon its introduction in the 1980s, causing increases in emergency department admissions for cocaine overdose, drug-related deaths, and births of cocaine-dependent babies. Administration of cocaine quickly produces intense euphoria, accompanied by a sense of increased energy, alertness, and self-confidence and diminished need for food and sleep. Pulse, blood pressure, and respiratory rate are increased. Higher doses can lead to bizarre or violent behavior, paranoia, chest pain, tremors, seizures, coma, and death due to coronary artery spasm or respiratory arrest. Smoked crack cocaine reaches the brain more quickly than snorted cocaine. The effects of either

form wear off in less than 30 minutes, to be succeeded by profound depression, irritability, and fatigue (“coke crash”). Prolonged use of cocaine leads to chronic symptoms including restlessness, irritability, depression, insomnia, and a reversible psychosis characterized by paranoia, hallucinations, and delusions. Repeated snorting of cocaine causes rhinitis, which can culminate in perforation of the nasal septum. Cocaine is not truly addictive because tolerance does not develop; in fact, some regular users note increasing sensitivity to its physical and psychologic effects. But psychological dependency can develop in less than 2 weeks. Withdrawal is associated with intense craving for another dose; sustained abstinence may lead to anxiety, depression, and disorders of appetite and sleep. crack c. a derivative of cocaine, usually smoked, resulting in a brief, intense high. Crack is relatively inexpensive and extremely addictive. See street drug. c. hydrochloride a water-soluble salt used for local anesthesia of the eye or mucous membranes.

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